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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/445,328	12/07/1999	KUBER T. SAMPATH	CIBT-P01-514	9813

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EXAMINER	
ROMEO, DAVID S	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 07/12/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/445,328	SAMPATH ET AL.	
	Examiner	Art Unit	
	David S Romeo	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,5,6,8-12,14-38,53 and 54* is/are pending in the application.

4a) Of the above claim(s) *21,22,25 and 28-34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,5,6,8-12,14-20,23,24,26,27,35-38,53 and 54* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *2,5,6,8-12,14-38,53 and 54* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 01/16/2004 has been entered.

Claims 2, 5, 6, 8, 9, 10, 11, 12, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 53, 54 are pending. Applicant's election with traverse of Group X, the species OP-1, the species the mature form of OP-1, the species pre-renal causes of acute renal failure, the species decreased cardiac output, and the species intravenous administration in Paper No. 12 is acknowledged. Claims 21, 22, 25, 28-34 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention and/or species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 12. Claims 2, 5, 6, 8, 9, 10, 11, 12, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 53, 54 are being examined only to the extent they read upon the elected invention and/or species.

Applicant's arguments with respect to claims 2, 5, 6, 8, 9, 10, 11, 12, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 53, 54 have been considered but are moot in view of the new ground(s) of rejection.

New Formal Matters, Objections, and/or Rejections:

Claim Rejections - 35 USC § 103

Claims 2, 5, 6, 8, 9, 10, 11, 12, 14, 23, 24, 26, 27, 35, 36, 37, 38, 53, 54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kelly (U) in view of Kuberasampath (AG, cited by Applicants) and Lefer (V).

Kelly discloses that mutant mice genetically deficient in ICAM-1 are protected from acute renal ischemic injury as judged by serum creatinine, renal histology, and animal survival. Renal leukocyte infiltration, quantitated morphologically and by measuring tissue myeloperoxidase, was markedly less in ICAM-1-deficient than control mice. Neutrophil-depleted normal mice were also protected against ischemic renal failure. ICAM-1 is a key mediator of ischemic acute renal failure likely acting via potentiation of neutrophil-endothelial interactions. See the Abstract. Kelly proposes that the protection afforded by knockout of the ICAM-1 gene is due to prevention of leukocyte accumulation in the kidney (page 1061, right column, full paragraph 1). The data of Kelly suggest that agents designed to block leukocyte-endothelial interactions mediated via ICAM-1 may be therapeutically effective in the prevention and treatment of acute renal failure (page 1062, left column, full paragraph 2). These data suggest a critical role for leukocytes and adhesion molecules, in particular ICAM-1, in the pathophysiology of ischemic acute renal failure and may have important therapeutic implications for the treatment of acute renal failure in humans (page 1062, left column, full paragraph 3). Kelly does not teach, in the sense that Kelly does not anticipate, administering OP-1 to a mammal afflicted with acute renal failure.

Kuberasampath teaches that damage to cells resulting from the effects of an inflammatory response by immune cell mediated tissue destruction has been implicated as the cause of reduced tissue function or loss of tissue function in the kidney; glomerulonephritis is believed to result in large part from unwanted acute inflammatory reactions and fibrosis (page 1, lines 21-33). The immune-cell mediated tissue destruction often follows an initial tissue injury or insult. The secondary damage, resulting from the inflammatory response, often is the source of significant tissue damage. Adhering neutrophilic leukocytes produce the humoral factors thought to mediate these damaging effects. Page 2, full paragraph 1.

It is well known that damage occurs to cells in mammals which have been deprived of oxygen. In fact, the interruption of blood flow, whether partial (hypoxia) or complete (ischemia) and the ensuing inflammatory responses may be the most important cause of coagulative necrosis or cell death in human disease. The complications of atherosclerosis, for example, are generally the result of ischemic cell injury in the brain, heart, small intestines, kidneys, and lower extremities. Highly differentiated cells, such as the proximal tubular cells of the kidney, cardiac myocytes, and the neurons of the central nervous system, all depend on aerobic respiration to produce ATP, the energy necessary to carry out their specialized functions. When ischemia limits the oxygen supply and ATP is depleted, the affected cells may become irreversibly injured. The ensuing inflammatory responses to this initial injury provide additional insult to the affected tissue. Examples of such hypoxia or ischemia are the partial or total loss of blood supply to the body as a whole, an organ within the body, or a region within an

organ, such as occurs in cardiac arrest, pulmonary embolus, renal artery occlusion, coronary occlusion or occlusive stroke. Page 3, full paragraph 1.

Kuberasampath provides a method for protecting mammalian tissue, particularly human tissue, from the damage associated with the inflammatory response following a tissue injury. Kuberasampath provides a method for alleviating tissue damage associated with ischemic-reperfusion injury in a mammal following a deprivation of, oxygen to a tissue in the mammal. Kuberasampath provides a method for modulating the inflammatory responses in general, particularly those induced in a human following tissue injury. Kuberasampath provides a method for alleviating tissue damage associated with ischemic-reperfusion injury in a human which has suffered from hypoxia or ischemia following cardiac arrest, pulmonary embolus, renal artery occlusion, coronary occlusion or occlusive stroke. Page 7, line 10, through page 8, line 19.

The method comprises the step of administering to the animal a therapeutically effective amount of a morphogenic protein upon tissue injury, for a time and at a concentration sufficient to significantly inhibit or reduce the tissue destructive effects of the inflammatory response. Page 9, full paragraph 1.

The methods comprise administering to a mammal a morphogenic protein upon injury to a tissue, or in anticipation of such injury, for a time and at a concentration sufficient to inhibit the tissue destructive effects associated with the body's inflammatory response, including repairing damaged tissue, and/or inhibiting additional damage thereto. Page 9, full paragraph 2.

OP-1 is a morphogen that is useful in the method (page 14, full paragraph 1). Kuberasampath also teaches the mature form of human OP-1 (page 15, lines 1-2), which comprises residues 330-341 of human OP-1.

When tissue injury occurs, the body's inflammatory response is stimulated. In response to signals released from the damaged cells, extravascularization of immune effector cells is induced. The vascular endothelium constitutes the first barrier between circulating immune effector cells and extravascular tissues. Extravasation of these circulating cells requires that they bind to the vascular endothelial cells, cross the basement membrane, and enter insulted tissues. It is believed that the morphogens may modulate the inflammatory response by modulating the attachment of immune effector cells to the luminal side of the endothelium of blood vessels at or near sites of tissue damage and/or inflammatory lesions. Because the method reduces or prevents the attachment of immune effector cells at these sites, it also prevents the subsequent release of tissue destructive agents by these same immune effector cells at sites of tissue damage and/or inflammatory lesions. Because attachment of immune effector cells to the endothelium must precede their extravascularization, the method also prevents the initial or continued entry of these cells into extravascular sites of tissue destruction or ongoing inflammatory lesions. Therefore, the method not only relates to a method to reduce or prevent the immune cell-mediated cellular destruction at extravascular sites of recent tissue destruction, but also relates to a method to prevent or reduce the continued entry of immune effector cells into extravascular sites of ongoing inflammatory cascades. As will be appreciated by those skilled in the art, the morphogens of this method also may be contemplated in mechanisms for disrupting the functional interaction of immune effector

cells with endothelium where the adhesion molecules are induced by means other than in response to tissue injury. Page 38, line 3, through page 40, line 9.

In addition to inhibiting the tissue destructive effects associated with the inflammatory response, the morphogens further enhance the viability of damaged tissue and/or organs by stimulating the regeneration of the damaged tissue. Page 40, full paragraph 2.

The morphogen may be provided parenterally, such as by intravenous injection (page 51, lines 8-9). Typical dose ranges are given (paragraph bridging pages 59-60). In addition, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation. OP1 (page 14, line 30, through page 15, line 17) inhibits the adherence of LTB4 activated PMNs to endothelium (Example 5, pages 74-75) and inhibits cellular and humoral inflammatory reactions (Example 7, pages 78-80). Kuberasampath also teaches that the tissues and organs for transplantation are also subject to the tissue destructive effects associated with the recipient's inflammatory response following transplantation (page 4, full paragraph 1). This tissue damage may occur following initiation of blood flow after transplantation (page 7, full paragraph 1).

Lefer teaches that hOP-1 exhibits significant anti-adherent actions on PMNs (page 592, left column, second sentence.

Kuberasampath and Lefer do not teach administering OP-1 to a mammal afflicted with acute renal failure (ARF).

However, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to administer an agent designed to block leukocyte-endothelial

interactions to a mammal afflicted with ARF, as taught by Kelly, and to modify that teaching by administering OP-1, as taught by Kuberasampath, with a reasonable expectation of success. One of ordinary skill in the art would be motivated to make this modification because agents designed to block neutrophil-endothelial interactions may be therapeutically effective in the prevention and treatment of acute renal failure and OP-1 blocks neutrophil-endothelial interactions.

To the extent that OP-1 reduces or prevents the immune cell-mediated cellular destruction at extravascular sites of recent tissue destruction, prevents or reduces the continued entry of immune effector cells into extravascular sites of ongoing inflammatory cascades, disrupts the functional interaction of immune effector cells with endothelium where the adhesion molecules are induced by means other than in response to tissue injury, to the extent that the ensuing inflammatory responses to an initial injury provide additional insult to the affected tissue and the damage to cells resulting from the effects of an inflammatory response by immune cell mediated tissue destruction has been implicated as the cause of reduced tissue function or loss of tissue function in the kidney, and to the extent that in addition to inhibiting the tissue destructive effects associated with the inflammatory response, the morphogens further enhance the viability of damaged tissue and/or organs by stimulating the regeneration of the damaged tissue, then one of ordinary skill in the art would have a reasonable expectation that administration of OP-1 to a mammal afflicted with acute renal failure would thereby delay the need for, or reduce the frequency of, dialysis treatments of a mammal afflicted with acute renal failure or thereby delay, prevent, inhibit, or alleviate permanent or progressive loss of renal function in the mammal afflicted with acute renal failure. Furthermore, such

expressions of delaying, reducing, preventing, inhibiting, and alleviating do not distinguish the claimed method from the prior art. The fact that Applicants have recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious.

If it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to administer OP-1 to mammal afflicted with acute renal failure, then it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to administer OP-1 to mammal afflicted with acute renal failure, wherein said mammal is a kidney transplant recipient or possesses only one kidney, with a reasonable expectation of success. One of ordinary skill in the art would be motivated to make this combination in order to treat the renal failure.

The limitation "wherein said renal therapeutic agent: ... acute renal failure," (claims 2, 53) and claim 54 only limit the properties of the agent administered and do not limit the method. The OP-1 taught by the prior art is identical to the OP-1 administered in the claimed method. Products of identical chemical composition can not have mutually exclusive properties. A chemical composition and its properties are inseparable. Therefore, the properties of the agent administered that applicant discloses and/or claims are necessarily present in the OP-1 taught by the prior art. Applicant is advised that should the claims be amended to require a process step encompassed by the presently claimed properties of the agent administered, a species election will be required. Applicant is further advised that where only generic claims are first presented and prosecuted in an application in which no election of a single invention has been

made, and applicant later presents species claims to more than one species of the invention, he or she must at that time indicate an election of a single species. Applicants can avoid a delay in prosecution by indicating an election of a single species if such an amendment is made.

The invention is prima facie obvious over the prior art.

Claims 2, 15-20, 53 rejected under 35 U.S.C. 103(a) as being unpatentable over Kelly (U) in view of Kuberasampath (AG, cited by Applicants) and Lefer (V) as applied to claims 2, 53 above, and further in view of Anderson (U, Paper No. 14) and Brady (W).

Kelly in view of Kuberasampath and Lefer teach administering OP-1 to mammal afflicted with acute renal failure. Kelly in view of Kuberasampath and Lefer are silent with respect to impaired cardiac output and serial determination of BUN and creatine.

Anderson teaches that impaired cardiac output is a major cause of acute deterioration in renal function (page 1293, Table 275-1). In acute renal failure the daily increments in BUN and serum creatinine average from 10 to 20 and 0.5 to 1.0 mg per 100 ml, respectively, to 40 to 100 and 2 to 5 mg per 100 ml, respectively (page 1296, left column, full paragraph 2). There has been an increasing tendency to use dialysis therapy early in acute renal failure (page 1298, left column, last full paragraph).

Low cardiac output is one of the major causes of prerenal ARF. See Brady, Page 1266, Table 236-1. Severe or prolonged hypoperfusion may lead to intrinsic renal azotemia (page 1266, left column, full paragraph 1). Management of acute renal failure should focus on elimination of the causative hemodynamic abnormality or toxin, avoidance of additional insults, and prevention and treatment of complications (page

1272, right column, full paragraph 3). Dialysis treatment is a supportive treatment of intrinsic acute renal failure (page 1273, TABLE 236-3).

Anderson and Brady do not teach administering OP-1 to a mammal afflicted with acute renal failure.

However, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to administer OP-1 to mammal afflicted with acute renal failure, as taught by Kelly in view of Kuberasampath and Lefer, and to modify that teaching by administering OP-1 to mammal afflicted with acute renal failure, wherein the mammal is afflicted with impaired cardiac output, with a reasonable expectation of success. One of ordinary skill in the art would be motivated to make this modification because impaired cardiac output is a major cause of acute deterioration in renal function and the management of acute renal failure should focus on elimination of the causative hemodynamic abnormality or toxin, avoidance of additional insults, and prevention and treatment of complications.

Anderson is evidence that the serial determination of BUN and creatine are routine and well known in the art.

The invention is prima facie obvious over the prior art.

Conclusion

No claims are allowable.

ANY INQUIRY CONCERNING THIS COMMUNICATION OR EARLIER COMMUNICATIONS FROM THE EXAMINER SHOULD BE DIRECTED TO DAVID S. ROMEO WHOSE TELEPHONE NUMBER IS (571) 272-0890. THE EXAMINER CAN NORMALLY BE REACHED ON MONDAY THROUGH FRIDAY FROM 7:30 A.M. TO 4:00 P.M. IF ATTEMPTS TO REACH THE EXAMINER BY TELEPHONE ARE UNSUCCESSFUL, THE EXAMINER'S SUPERVISOR, BRENDA BRUMBACK, CAN BE REACHED ON (571)272-0961.

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ANY INQUIRY OF A GENERAL NATURE OR RELATING TO THE STATUS OF THIS APPLICATION OR PROCEEDING SHOULD BE DIRECTED TO THE GROUP RECEPTIONIST WHOSE TELEPHONE NUMBER IS (703) 308-0196.

DAVID ROMEO
PRIMARY EXAMINER
ART UNIT 1647

DSR
JULY 9, 2004